Role of Endothelial Dysfunction in Thrombus Formation in the Left Atrium
– Protective Role of Nitric Oxide Synthesis in the Surface of Atrium –
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What Is the Mechanism of Thrombus Formation in the LA In Vivo?
Coagulation and hemostasis are the most fundamental and important functions of human blood, protecting multiple organs from severe hemorrhage of various etiologies. Not only stimulation of coagulation factor VII by tissue factor, but also various other stimuli as well as platelet aggregation can quickly lead to the formation of large thrombus because that is the basic function of the hemostatic system. On the other hand, the vascular system must promote smooth blood flow in all parts of the body, so an intrinsic anticoagulation system has to be present. It is well known that the vascular endothelium plays a key role in preventing thrombus formation by mechanically protecting platelets from stimuli from extravascular tissue, and also by secreting various anticoagulation factors, such as thrombomodulin, heparin sulfates, prostacyclin, nitric oxide (NO), tissue plasminogen activator, etc, to protect against unnecessary activation of coagulation factors. Table summarizes the function and mechanisms of the antithrombotic effect of the vascular endothelium, and the normal vascular wall in protecting blood flow from inappropriate thrombus formation. Although several reports have already documented that vascular endothelial dysfunction can lead to thrombus formation, especially at the site of atherosclerosis through reduction of any of the aforementioned anticoagulation factors, the mechanism of thrombus formation in the atrium, especially the left atrium (LA), is still unclear. The structure of the atrial wall is different from that of the vascular wall, but the reduction of similar anticoagulation factors, including thrombomodulin, NO, and tissue plasminogen activator, or upregulation of plasminogen activator inhibitor-1, has been documented in the LA wall in the elderly in whom a hypercoagulation state can be speculated. Thus, endothelial dysfunction is probably involved, at least in part, in the mechanism of thrombus formation in the LA.

Unique Model of LA Thrombus Formation
The difficulty with investigating the mechanism of LA thrombus formation is mainly related to the lack of a feasible in-vivo model of atrial thrombus. In this issue of the Journal, Mawatari et al document enhanced LA thrombus formation in a unique model of SPORTS (Spontaneously-Running Tokushima-Shikoku) rats. Although it is not a model of atrial fibrillation or any atrial dysrhythmia, establishment of a LA thrombus model is extremely important for advancing the investigation of the mechanism of atrial thrombus formation. In their report, they found LA endothelial dysfunction and reduction of endothelial NO synthesis, and concluded that the reduction in eNOS expression is the main mechanism of LA thrombus formation.

Additional Mechanism of LA Thrombus Formation
There might be additional mechanisms of LA thrombus formation, even in this model. Unfortunately, Mawatari et al did not find any other significant findings to explain the mechanism of LA thrombus formation, except for the reduction in eNOS expression. Additional mechanisms might be sought in future studies.

Table. Antithrombotic Mechanisms of the Vascular Endothelium

<table>
<thead>
<tr>
<th>Substance</th>
<th>Action</th>
<th>Antithrombotic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TM</td>
<td>Capture of thrombin</td>
<td>Suppression of coagulation factors</td>
</tr>
<tr>
<td>TM</td>
<td>Change protein C to activated form (APC)</td>
<td>Suppression of coagulation factors</td>
</tr>
<tr>
<td>Heparin sulfate</td>
<td>Contains AT &amp; TFPI</td>
<td>Suppression of coagulation factors</td>
</tr>
<tr>
<td>AT</td>
<td>Inhibition of factor II</td>
<td>Suppression of coagulation factors</td>
</tr>
<tr>
<td>TFPI</td>
<td>Inhibition of factor VII</td>
<td>Suppression of coagulation factors</td>
</tr>
<tr>
<td>PGI2</td>
<td>Antiplatelet aggregation</td>
<td>Antiplatelet aggregation</td>
</tr>
<tr>
<td>NO</td>
<td>Vasodilatation</td>
<td>Decreased shear stress</td>
</tr>
<tr>
<td>IPA</td>
<td>Change plasminogen to plasmin</td>
<td>Fibrinolysis</td>
</tr>
</tbody>
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AT, antithrombin; NO, nitric oxide; PGI2, prostacyclin; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; IPA, tissue plasminogen activator.
not evaluate changes in the other anticoagulation or exaggerating factors, but a reduction in other anticoagulation factors could be involved as the mechanism. Additionally, because SPORTS rats exhibit marked thickening of the LA free wall, hyper-expression of von Willebrand factor can be induced and might result in a hypercoagulable state. Although typical histological finding of local inflammation (ie, infiltration of mononuclear cells) was not observed, various degrees of inflammation can be induced and such stimulation can lead to a local coagulation imbalance on the LA endocardial surface. Because such changes cannot be separated completely from other factors, it can be speculated that changes in such various factors would be involved in the mechanism of LA thrombus formation. Because those authors documented that replenishment of NO synthesis through the administration of L-arginine almost completely recovered the hyper-state for LA thrombus formation, it seems to be fair to conclude that a reduction in NO synthesis was the main mechanism of thrombus formation at least in this model. But the real mechanisms of LA thrombus formation, which may be an imbalance of coagulation and anticoagulation states, should be solved in future studies using this unique model of LA thrombus formation.

References